IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: JOHN F. T. CONROY, M.E. POWER, AND P. M. NORRIS

Serial No.:	09/785,188	Art Unit:	1651
Filed:	February 20, 2001	Examiner:	David M. Naff
Title:	SOL-GEL BIOMATERIAL IMMOBILIZATION		

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Commissioner for Patents
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BRIEF ON APPEAL

(1) Real Party in Interest

The real parties in interest in the application are the joint assignees John F. Conroy, a real person residing in California, Mary E. Power, a real person residing in Canada, and Pamela M. Norris, a real person residing in Virginia.

(2) Related Appeals and Interferences

The applicants are not aware of any appeals and/or interferences related to the application.

(3) Status of Claims

Claims 1-29 and 31-39 are pending in this application.

Claims 1-14 and 27 have been withdrawn from consideration.

Claims 15-26, 28, 29, and 31-39 have been finally rejected in the Office action dated August 24, 2004.

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(4) Status of Amendments

No amendment has been filed after final rejection.

(5) Summary of Invention

Background:

Sol-gel-derived materials such as silica have been investigated by several researchers as cytocompatible scaffolds for the immobilization of cells. *See* specification, page 1, line 28 – page 2, line 24 and the references cited therein. These investigations have been spurred by several favorable characteristics of sol-gel-derived materials as immobilization matrices. These characteristics include low temperature production routes, chemical-, temperature-, and radiation-stability, high surface area and porosity, ease of functionalization, mechanical rigidity (little or no swelling), and tunable properties and microstructures. *See* specification, page 1, line 19–25.

Despite this promise of sol-gel-derived materials, limited progress in the use of sol-gel-derived materials as a cell immobilization matrices has been made. *See* specification, page 2, line 25–26. Common sol-gel production methods are too cytotoxic at the time of gelation for extensive use in the immobilization of cells. Furthermore, macroporous samples amenable to colonization are difficult to obtain and require the use of toxic chemicals. *See* specification, page 2, line 27 – page 3, line 22 and the references cited therein.

The Present Application:

The present disclosure describes methods and compositions suitable for the immobilization of even fragile microorganisms in macroporous sol-gel-derived cell immobilization matrices.

To address the cytotoxicity of common sol-gel production routes, the inventors have developed novel routes in which organic solvent is removed before the addition of microorganisms. To compensate for the volume decrease associated with the removal of the organic solvent and to allow macroporous gels to be obtained, the inventors have developed high water content production routes that use higher hydrolysis ratios than the vast majority of sol-gel production routes. *See* specification, page 5, line 14–16 and the references cited therein. Further, rather than following other researchers and adding additional non-polar organic solvent

to the pre-gelation sol so that gel precursors can be solvated in a relatively polar, high hydrolysis ratio aqueous phase, the inventors have realized that an alkoxy silicate can be hydrolyzed in a low pH aqueous solution until it is sufficiently polar to dissolve in the aqueous solvent. Once dissolution has occurred, the hydrolyzed sol is amenable to further manipulation for specific applications. This manipulation can include the gelation of macroporous matrices that are amenable to colonization by microorganisms.

(6) Issues

The issues to be decided on appeal are:

I. Are claims 26 and 29 obvious over the publication of Uo et al. (J. Ceram. Soc. Jpn. Vol. 100, p. 426-429, hereinafter "Uo") and U.S. Patent No. 4,148,689 to Hino et al. (hereinafter "Hino")?

II. Is claim 28 obvious over Uo and Hino?

III. Is claim 15 obvious over Uo, Hino, the publication of Klein et al. (Better Ceramics Through Chemistry: MRS Symp. Proc. Vol. 32, p. 33-39, hereinafter "Klein"), and the publication of Rao et al. (J. Sol-Gel Sci. Tech. 3, p. 205-217, hereinafter "Rao").

(7) Grouping of Claims

Claims 15-26, 28, 29, and 31-39 do not stand or fall together.

Rather, claims 26, 29, and 31-36 stand or fall together;

claim 28 stands or falls independently; and

claims 15-25 and 37-39 stand or fall together.

In dealing with a method and a gel that involve a vegetative cell, claims 26 and 29 are separately patentable from claim 28 (which deals with a gel including a bacterial cell) and claim 15 (which deals with biological materials in a sol where the ratio of moles of water to moles of hydroxy metallate is greater than 25:1). Claim 28 is also separately patentable from claim 15 in that the gel of claim 28 is not necessarily formed from the sol of claim 15.

(8) Argument

I. Claims 26 and 29 are not Obvious over Uo and Hino

<u>A *Prima Facie* Case of the Obviousness of Claims 26 and 29 over Uo and Hino has not been Established</u>

Independent claims 26 and 29 stand rejected under 35 U.S.C. § 103(a) as obvious over Uo and Hino.

Claim 26 relates to a method that includes mixing a vegetative cell into a sol, mixing a sufficient amount of a dispersant into said sol to cause macropores in a gel formed by the sol; and gelling the sol to form the gel. Claim 29 relates to a gel that includes a solid network formed by the condensation of hydroxy metallates from a sol solution and a vegetative cell added to the sol solution and thereby immobilized within said solid network. The solid network defines macropores.

In the rejections of claims 26 and 29, it has been asserted that it would have been obvious to substitute the vegetative cells described by Hino for the yeast spores immobilized in Uo's macroporous gels. Applicants respectfully disagree, and instead submit that one of ordinary skill would not be motivated to combine the references in this manner. In particular, one of ordinary skill would expect Uo's gelation solution to be toxic to Hino's vegetative cells and thus would not have a reasonable expectation of success with the combination.

Support for the position that one of ordinary skill would expect Uo's gelation solution to be toxic to Hino's vegetative cells is found in Uo, in a technical understanding of the antimicrobial activity of alcohols, and in Hino.

Uo himself suggests that his gelation solutions would be toxic to vegetative cells. In particular, Uo describes that the gelation solutions he uses to form macroporous gels require robust immobilants (i.e., yeast spores), rather than vegetative yeast or other cells. Uo has chosen the robust yeast spores for immobilization due to their durability to organic solvents. See Uo, Section 2.2, page 427.

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the appellant." *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994). The totality of a reference's teachings must be considered when determining if a reference teaches away. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550-51 (Fed.Cir.1983), cert. denied, 469 U.S. 851 (1984). "As a

'useful general rule,' ... references that teach away cannot serve to create a prima facie case of obviousness." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339 (Fed. Cir. 2001).

The rejection has never indicated why this general rule is to be ignored in this case. The express language in Uo clearly states that robust yeast spores are needed to endure Uo's gelation solutions. To discard Uo's express teaching away from vegetative cells is to engage in hindsight-based reconstruction of applicants' invention, without due consideration of the express teachings of Uo as a whole. As such, there is no reasonable expectation of success and, on this basis alone, a *prima facie* case of obviousness has not been established.

A technical understanding of the antimicrobial activity of alcohols also suggests to one of ordinary skill that Uo's gelation solutions would be toxic to vegetative cells. Alcohols, such as the methanol present in the sol solutions of Uo, have long been recognized as effective antimicrobial agents. See, e.g., Chapter 12 of the 5th Edition of *Disinfection, Sterilization, and Preservation* edited by Seymour Block[1] (submitted with the Response filed July 25, 2003), which discusses the antimicrobial properties of alcohols in general, and methanol in particular, toward, e.g., both vegetative bacteria[2] and bacterial spores.[3] Assuming that the spore suspensions of Uo are entirely water and that the tetramethylorthosilicate (TMOS) in the starting solution completely prehydrolyzes,[4] Uo's gelation solutions are approximately 45-55 vol.% methanol.[5] The yeast spores in Uo are exposed to these solutions for over one day. Attention is respectfully directed to table 12.4 on page 235 of Block which describes that 65 vol.% methanol is microbicidal to both *Staphylococcus aureus* and *Escherichia coli* in <u>under one minute</u> in suspension tests, and that even 9 vol.% methanol is effective at inhibiting *S. aureus* growth. Attention is further directed to table 12.7 on page 236 of Block which illustrates that germicidal

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[1] Lippincott Williams & Wilkins, Philadelphia, PA, U.S.A. (2001).
[2] Page 234-238 of Block.
[3] Page 238-239 of Block.
[4] Uo et al. prehydrolyze starting solutions for 1 day at 20°C in sealed containers. See, e.g., section 2.3 of Uo et al.
[5] Attention is respectfully directed to Table 3 of Uo et al. which lists the compositions of starting solutions for the immobilization of yeast spores. If one assumes that the spore suspension is entirely water, then Composition A includes approximately 17 moles of water, and Composition B includes approximately 11 moles of water. After complete hydrolysis of the TMOS in the starting solution, Compositions A and B each include approximately 6 moles of methanol (2 moles added and 4 moles released by hydrolysis of 1 mole of TMOS). The methanol/water molar ratios of Compositions A and B before spore addition are approximately 6:17 and 6:11, respectively. Methanol has a gram molecular weight of 32.04 g/mol and a density of 0.791 g/mL. Water has a gram molecular weight of 18.02 g/mol and a density of 1.0 g/mL. Neglecting volume contraction, Compositions A and B each include approximately 243 mL of methanol, Composition A includes approximately 298 mL of water, and Composition B includes approximately 193 mL of water.

activity can be achieved with decreased concentrations of ethanol when exposure time is increased.

"The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, *viewed in the light of the prior art.*" *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (emphasis added). "In determining whether such a suggestion can fairly be gleaned from the prior art, the *full field of the invention must be considered*; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." *Id.* (emphasis added). "The PTO *must also give weight* to objective evidence of non-obviousness during patent prosecution." *In re Sernaker*, 702 F.2d 989, 996 (Fed.Cir.1983) (emphasis added).

It is respectfully submitted that, in the present case, the technological literature itself suggests to one of ordinary skill that Uo's gelation solutions would be toxic to vegetative cells. Moreover, the rejection does not give the technological literature its due weight, nor has any grounds for ignoring the express teachings of the technical literature ever been presented. It is therefore respectfully submitted that a *prima facie* case of obviousness has not been established.

Hino himself also describes that his vegetative cells are susceptible to the antimicrobial activity of alcohols. In particular, Hino describes that sols containing cells can be extrusion cast into organic solvents. See col. 20, lines 44-45 and col. 9, line 14-22 of Hino. In the example of extrusion casting detailed by Hino, the gels were freeze-dried immediately after extrusion and the relative activity of *Erwinia herbicola* after casting in isopropyl alcohol was approximately 61% of the control activity, whereas activities of 84-90% of control were obtained without casting. See, e.g., Tables 6 and 7, and col. 14, line 54-col. 16, line 22. It appears that the immediate freeze drying represents an attempt by Hino to minimize exposure of *E. herbicola* to isopropyl alcohol (due to microbicidal activity of isopropyl alcohol described, e.g., in tables 12.4 and 12.5 on page 235 of Block). Further, even this attempt was only partially successful since a decrease in activity relative to uncast gels was observed.

Once again, the rejection has never indicated why the "useful general rule" precluding the use of references that teach away when establishing a *prima facie* case of obviousness is to be ignored. Hino clearly implies that contact between Hino's vegetative cells and alcohols is to be avoided and expressly states that even the minimal contact that occurs with immediate freeze

drying results in decreased biological activity. To pretend that one of ordinary skill would ignore these teachings is to engage in hindsight-based reconstruction of applicants' invention, without due consideration of the teachings of Hino as a whole. As such, there is no reasonable expectation of success and, on this basis alone, a *prima facie* case of obviousness has not been established.

Despite the establishment of three independently sufficient reasons why the rejection of claims 26 and 29 as obvious is improper, the rejections have never asserted even a pretextural ground for contending that the prior art would lead one of ordinary skill to combine Hino's vegetative cells with Uo's gelation solutions for macroporous gels with a reasonable expectation of success. The closest thing to such an assertion is found on page 4 of the action mailed August 24, 2004, which contends that the use of vegetative bacterial cells would have been obvious since bacterial cells are normally found in this state. However, this assertion neglects the well-established requirement that the suggestion to combine must be found with a *reasonable expectation of success*. Since both Hino and Uo (as well as an understanding of the antimicrobial activity of alcohols) lead to the exact opposite conclusion (i.e., that there is no expectation of that Hino's vegetative cells would survive Uo's gelation solution), there is no suggestion to combine founded in the prior art. This lack of even a pretextural suggestion to combine is yet another independently sufficient reason that a *prima facie* case of obviousness has not been established.

<u>Other Contentions Raised in Rejecting Claims 26 and 29</u>

Instead of seeking to establish a *prima facie* case of obviousness, a series of contentions have been made that have been thought to bear on the patentability of claims 26 and 29. For the sake of completeness, applicants now respond to these contentions.

A first such contention is that the present claims do not exclude an organic solvent and do not exclude the harmful effects of solvent on the cells. *See, e.g.,* page 5, line 1-8 of the action mailed August 24, 2004.

Applicants respectfully submit that the fact that the present claims do not exclude organic solvent is irrelevant. Applicants are entitled to claims as broad as the prior art and applicants' disclosure will allow. *In re Rasmussen*, 650 F.2d 1212, 1214 (Cust. & Pat.App. 1981). To hold otherwise would be to oblige applicants to claim the reasons why the references teach away from their combination, or to claim the reasons why one of ordinary skill would not be motivated to

combine the references. To the best of Applicants' knowledge, no court has ever imposed such a requirement. Rather, the fact that the references teach away from their combination and that one of ordinary skill would not be motivated to combine the references with a reasonable expectation of success are, in and of themselves, sufficient to show that a *prima facie* case of obviousness has not been established.

A second such contention is that, if one ignores the toxicity of Uo's gelation solution toward vegetative cells, the use of Hino's vegetative cells in Uo's gelation solution is obvious. *See, e.g.,* page 5, line 8-9 of the action mailed August 24, 2004.

Applicant submits that nothing founded in the prior art would lead one of ordinary skill to ignore the toxicity of Uo's gelation solution toward vegetative cells. Uo did not ignore the toxicity of his solution toward vegetative cells and selected yeast cells for their robustness. The hospitals and medical personnel that relied on alcohols to sterilize equipment for decades did not ignore the toxicity of alcohols toward vegetative cells. See, e.g., page 229 of Block. With his immediate freeze drying after extrusion into alcoholic solution, Hino also appears not to have ignored the toxicity of alcohols toward his vegetative cells. Accordingly, Applicants submit that one of ordinary skill would not blithely ignore the toxicity of Uo's gelation solution toward vegetative cells.

A third such contention is that Hino suggests that the organic solvent can be omitted from forming a "gel substantially as Uo." *See, e.g.,* page 5, line 10-12 of the action mailed August 24, 2004.

Applicant disagrees. Hino fails to describe or suggest forming a *macroporous* gel like Uo's. Instead of macroporous gels, the pores in the overwhelming majority of Hino's gels are so small that the gels are either transparent or the color of immobilized cells. Transparent and colored gels do not scatter or reflect visible wavelength (approx. 400 nm to approx. 700 nm) light. Since these gels do not scatter or reflect visible wavelength light, their *pores are inherently smaller than macropores*. See, e.g., Hino, col. 10, line 20-21 ("a colorless, transparent homogeneous complex lyogel was formed" from a solution containing 50 g of 10% PVA), col. 10, line 25-26 ("complex lyogel [formed from a solution containing 50 g of 10% PVA] ... also was transparent"), col. 10, line 45-46 ("appearance of resulting lyogel [from solution containing 50 g of 10% PVA] were almost the same"), col. 10, line 55-57 ("lyogel was

again formed [from a solution containing 50 g of 10% PVA] and was found to have similar appearance (i.e. was colorless and transparent)").

In Hino, *every gel that includes a cell is the color of the immobilized cells* and hence does not scatter visible wavelength light. See, e.g., Hino, col. 13, line 4-5 ("[a] yellowish brown film containing the yeast cells was obtained" from a solution containing 100 Parts of 10% PVA), col. 13, line 45-48 ("gel [from a solution containing 100 Parts of 10% PVA] was spread on a plate and dried by ventilation to obtain a yellowish brown film containing yeast cells"), col. 14, line 13-16 ("The gel, thus obtained [from a solution containing 100 Parts of 10% PVA], was spread on a plate and dried by ventilation at room temperature to obtain a yellowish brown film containing 1 g of yeast cells."). The pores in the gels with immobilized cells are thus smaller than macropores.

There are two gels in Hino that are not completely transparent or the color of immobilized cells and hence not explicitly excluded from including macropores. The first such gel is described at col. 12, line 6 of Hino as a "whitely turbid xerogel." This xerogel does not include a biological material. Moreover, this xerogel had been ventilation dried. Such drying both destroys the lyogel pore structure due to capillary forces and makes the xerogel more inhospital to biological materials. Finally, there is no indication by Hino that these pores are macropores. Rather, Hino simply describes that they scatter light.

The second gel not explicitly excluded from including macropores is described at col. 12, line 35 of Hino as a "semi-transparent complex lyogel." This lyogel does not include a biological material and there is no indication in Hino that such a gel can be formed to include a biological material. Moreover, it is respectfully submitted that given the pore sizes of Hino's other gels, this lyogel is most likely to scatter visible light only at the shorter wavelength end of the visible light spectrum and hence not include macropores.

Accordingly, Hino neither describes nor suggests that an organic solvent can be omitted when forming a macroporous gels like Uo's. Indeed, every reference of record teaches the exact opposite conclusion—namely that macroporous gels like those in Uo require toxic conditions. Uo required robust immobilants when forming his macroporous gels. United States Patent 4,148,689 to Nakanishi et al. (cited in the action mailed October 15, 2002) requires thermolysis with urea (or, e.g., formamides and acetamides) at temperatures between 60°C and 200°C and pH's between 9.0 and 11.0 to dissolve the walls of porous inorganic gels. Kajihara et al. in *J.*

Am. Ceram. Soc. 81, p. 2670-2676 (also cited in the action mailed October 15, 2002) describes the macroporous titania gels formed by gelation in a sol solution that contains between five and ten moles of ethanol for every mole water. Every reference of record describes toxic conditions during the formation of macroporous gels.

"In determining whether such a suggestion [to combine references] can fairly be gleaned from the prior art, *the full field of the invention must be considered*; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (emphasis added).

Accordingly, since neither Hino nor any other art of record describes or suggests that an organic solvent can be omitted when forming a macroporous gels, Applicants submit that one of ordinary skill would not conclude that organic solvent can be omitted when forming macroporous gels.

A fourth such contention is that, for claims 26 and 29 to be patentable, Applicants must establish that obtaining macropores using Uo's gelation solution depends on whether or not an organic solvent is present. See, e.g., page 5, line 14-17 of the action mailed August 24, 2004.

This contention neglects the fact that removing.the organic solvent from Uo's gelation solution will inherently yield a gelation solution that is not Uo's. In other words, the contention is moving outside the scope and content of the prior art. If Uo does not describe a gelation solution without an organic solvent, Uo cannot serve as a reference in establishing a rejection that requires a gelation solution without an organic solvent.

Further, Applicants are under no such burden to prove that Uo's solution does or does not require an organic solvent to form macropores. It is well-established that the burden of establishing a *prima facie* case of obviousness is on the Office. Since neither Uo nor any other art of record describes or suggests that an organic solvent can be omitted when forming a macroporous gels, Applicants submit that one of ordinary skill would not conclude that organic solvent can be omitted when forming macroporous gels.

A fifth such contention is that since Hino uses his gels in a flow-through column, the substrate must pass into the gel and the gel must therefore include macropores. See, e.g., page 5, line 22 – page 6, line 2 of the action mailed August 24, 2004.

This contention neglects the fact that Hino's gels are molded into shapes that establish *interstices outside the gel shapes*. Hino gels are molded after gelation into desired shapes that are "granular-type having a round section and in particularly may be spheres, granules, pellets, filaments and so on." It is this molding provides a "desirable flow rate of the reaction mixture through the column reactor." See Hino, col. 8, line 34 – col. 9, line 13.

Since spheres, granules, pellets, and filaments do not pack perfectly in the column volume (i.e., there are voids between the individual gel spheres, granules, pellets, and filaments), the reaction mixture can flow through the interstices between the shapes rather than through the gels. As such, flow through Hino's column is irrelevant to determining whether or not Hino's gels include macropores.

A sixth such contention is that the present specification discloses no way of avoiding the harmful toxicity of an organic solvent. See, e.g., page 6, line 7–8 of the action mailed August 24, 2004.

Applicant respectfully disagrees. For example, FIG. 1 illustrates that organic by-products of sol hydrolysis can be removed from the gelation solution, e.g., by distillation. Such a removal of organic by-products reduces the concentration of such by-products. A reduced concentration of organic by-products decreases the toxicity of the gelation solution, as evidenced by the immobilization results described in the application and the technical understanding described in Block.

In summary, both cited references, a technical understanding of the microbicidal properties of alcohols, and every other reference of record teach or lead away from the claims. Applicants therefore respectfully submit that claims 26 and 29, along with the claims dependent therefrom, are not obvious over Uo and Hino.

II. Claim 28 is not Obvious over Uo and Hino

A *Prima Facie* Case of the Obviousness of Claims 28 over Uo and Hino has not been Established

Independent claim 28 stands rejected under 35 U.S.C. § 103(a) as obvious over Uo and Hino.

Applicants respectfully traverse the rejection.

Claim 28 relates to a gel that includes a macroporous solid network and a bacterial cell. The macroporous solid network is formed by the condensation of hydroxy metallates from a sol solution. The bacterial cell is added to the sol solution and thereby immobilized within the solid network. The sol solution is compatible with the bacterial cell.

The rejection of claim 28 contends that it would have been obvious to replace the yeast spores in the macroporous solid network of Uo with bacterial spores, and therefore bacterial cells.

The rejection admits that neither Uo nor Hino describe bacterial spores at all. Since elements and/or limitations from claim 28 are not described in Uo and Hino, Applicants submit that a *prima facie* case of obviousness of claim 28 has not been established.

Further, as discussed above, Uo teaches away from exposure of organisms other than robust yeast spores to the kinds and concentrations of organic solvents found in the sols of Uo. Therefore, as a useful general rule, Uo cannot serve to create a *prima facie* case of obviousness. Hino teaches that the exposure of his bacterial cells to organic solvent for even short periods of time results in decreased activity, and hence away from a gel that includes his bacteria in a gel formed using Uo's gelation solution. Therefore, as a useful general rule, Hino also cannot serve to create a *prima facie* case of obviousness. Finally, an understanding of the antimicrobial activity of alcohols also suggests to one of ordinary skill that Uo's gelation solutions would be toxic to bacteria. *See, e.g.,* page 234-238 of Block.

Thus, in addition to the fact that elements and/or limitations relied upon in rejecting claim 28 are not described in the cited art, Applicant submits that there are three independently sufficient reasons why one of ordinary skill would make the proposed combination with a reasonable expectation of success.

Other Contentions Raised in Rejecting Claim 28

Instead of seeking to establish a *prima facie* case of obviousness, a series of contentions have been made that have been thought to bear on the patentability of claim 28. For the sake of completeness, applicants now respond to these contentions.

A first such contention is that, rather than individual bacterial cells, Hino actually describes a broad set of bacterial cell functions that are immobilized in gels. Since this set of bacterial cell functions can be, at least in part, performed by bacterial spores, Hino suggests that bacterial spores can be combined with Uo's gels. *See, e.g.,* page 6, line 14 of the action mailed August 24, 2004.

Applicant respectfully disagrees. One of the bacterial cell functions that is not described by Hino at all is sporulation, the exact function relied upon in rejecting claim 28. Since this function is not described by Hino, there is no reason to believe that one of ordinary skill in the art would be motivated to investigate bacterial spores to arrive at the proposed combination.

A second such contention is that the sol and gel forming methods of Hino and Uo are similar and therefore one of ordinary skill would be motivated to immobilize bacterial spores that are not described in either reference in Uo's gels. *See, e.g.,* page 6, line 13-16 of the action mailed August 24, 2004.

Applicants respectfully disagree with the contention that Uo's and Hino's gels are similar in a manner relevant to claim 28. In particular, Uo's gels are macroporous gels. As discussed above, the majority Hino's gels are expressly precluded from being macroporous. Since claim 28 relates to a gel that includes a macroporous solid network, Uo's and Hino's gels are dissimilar in the manner relevant to claim 28.

Applicants also disagree with any suggestion that any similarity in Uo's and Hino's gelation process would lead one of ordinary skill to immobilize bacterial spores, especially when bacterial spores are not described by either Uo or Hino. To the best of Applicants' understanding, and in light of the teachings of the cited art, there is simply no rational relationship between the alleged cause of the action (i.e., similarity in gels) and the action purportedly resulting from that cause (i.e., immobilizing bacterial spores).

A third such contention is that one of ordinary skill would rely upon Uo's teachings that his gelation solutions are toxic to vegetative yeast and would therefore immobilize bacterial spores using Uo's gelation solutions. *See, e.g.,* page 6, line 19-20 of the action mailed August 24, 2004.

This contention amounts to nothing more than hindsight-based reconstruction of Applicants' claims. Neither Uo nor Hino make any mention whatsoever of bacterial spores. Neither Uo nor Hino suggest that immobilizing bacterial spores in a macroporous solid network formed by the condensation of hydroxy metallates is a good idea. A conclusion of obviousness must be based on the scope and content of the prior art, rather than subjective feelings regarding what is or is not obvious. "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

Further, although Block describes that the sporicidal activity of alcohols against bacterial spores may be limited, alcohols are still sporicidal. See, e.g., page 238-239 of Block. One of ordinary skill would have to ignore this general knowledge regarding the sporicidal activity of alcohols to immobilize bacterial spores as suggested by the rejection.

Finally, Applicants submit that one of ordinary skill would expect even bacterial spores to be less successful in surviving Uo's gelation solution than the particular species of yeast spores immobilized by Uo. One of ordinary skill would expect the species of yeast immobilized by Uo *Saccharomyces cerevisiae* (i.e., "brewers yeast") to be especially resistant to alcohols, since brewers yeast ferments sugars to yield ethanol as part of its ordinary metabolic activity. Accordingly, one of ordinary skill would expect that other spores, such as the bacterial spores relied upon by the rejection, would be less resistant to alcohols. Accordingly, one of ordinary skill would not be motivated to immobilize such bacterial spores using Uo's gelation solution with a reasonable expectation of success.

A final such contention is that claim 28 does not expressly exclude an organic solvent. Applicants respectfully submit that the fact that the present claims do not exclude organic solvent is irrelevant. Applicants are entitled to claims as broad as the prior art and applicants' disclosure will allow. *In re Rasmussen*, 650 F.2d 1212, 1214 (Cust. & Pat.App. 1981). To hold otherwise would be to oblige applicants to claim the reasons why the references teach away from their combination, or to claim the reasons why one of ordinary skill would not be motivated to combine the references. To the best of Applicants' knowledge, no court has ever imposed such a requirement. Rather, the fact that the references fail to describe or suggest elements and/or

limitations relied upon in rejecting the claims is sufficient to show that a *prima facie* case of obviousness has not been established.

Applicants therefore submit that claim 28 is not obvious over Uo and Hino.

III. Claim 15 is not Obvious over Uo, Hino, Klein, and Rao

A *Prima Facie* Case of the Obviousness of Claims 15 over Uo, Hino, Klein, and Rao has not been Established

Independent claim 15 stands rejected under 35 U.S.C. § 103(a) as obvious over Uo, Hino, Klein, and Rao.

Applicants respectfully traverse the rejection.

Claim 15 relates to a sol that includes P moles of a hydroxy metallate, W moles of water, a sufficient amount of a dispersant to cause macropores in a gel formed by said sol, and a biological material. The ratio of W:P is greater than 25:1.

None of Uo, Hino, or Rao describe sol solutions with a water to hydroxy metallate ratio greater than 25:1.

Klein describes a sol solution with a water to hydroxy metallate ratio of 32:1. In Klein, the sol solutions with elevated water to hydroxy metallate ratios have additional ethanol to permit solubility of the increased water in the sol solution. *See* Klein, page 34, last sentence of the second paragraph. In particular, the sol solution with a W:P ratio of 32:1 has four times as much ethanol as the sol solutions with W:P ratios of 4:1. *See* Klein, page 34, second paragraph. Assuming that the tetraethylorthosilicate (TEOS) in the gelation solution completely prehydrolyzes, Klein's gelation solutions are approximately 65 vol.% ethanol.[6] The sol solutions of Klein were capped, heated to 80°C, and allowed to react for two days. Attention is respectfully directed to pages 231-232 of Block where alcohol-induced protein coagulation and plasma membrane lysis is described, table 12.6 on page 235 of Block which describes that 60-70

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[6] Attention is respectfully directed to paragraph 2, page 34 of Klein et al. which describes the compositions of sol solutions of varying hydrolysis ratios. The sol solution with a 32:1 molar ratio of water to TEOS includes a volume of ethanol that is four times the volume of TEOS. TEOS has a gram molecular weight of 208.3 g/mol and a density of 0.934 g/mL, as described in the specification for Sigma-Aldrich product number 13,190-3, tetraethyl orthosilicate, submitted with the response filed July 25, 2003. Thus, for 32 moles of water, the sol solution includes approximately 19.3 moles of ethanol (four moles of ethanol from complete hydrolysis of TEOS and 15.3 moles of ethanol from the 892 ml of ethanol added to solubilize 1 mole (223 ml) of TEOS with 32 moles of water). This ethanol/water molar ratio of 19.3:32 corresponds to an approximately 64 wt.% ethanol solution, which is greater then 65 vol.% ethanol, according to table 12.3 of Block.

vol.% ethanol is effective at killing a number of bacterial species in <u>under one minute</u>, pages 238-239 of Block where the sporicidal activity of ethanol is described, and table 12.10 on page 239 of Block where the viricidal activity of ethanol against a number of viral species is described in terms of minutes and hours. Attention is further directed to table 12.7 on page 236 of Block which illustrates that germicidal activity can be achieved with decreased concentrations of ethanol when exposure time is increased. It is further pointed out that the majority of these investigations were conducted either at room temperature or at physiological temperatures rather than the 80°C used in Klein.

The rejection contends that one of ordinary skill in the art would find a suggestion to combine Uo, Hino, Rao, and Klein based on an increased rate of hydrolysis with a higher amount of water despite the results described in Block. Neglecting the issue as to whether an increased rate of hydrolysis is relevant at all to the immobilization of biological materials, applicants respectfully submit that the suggestion to combine must be accompanied by a reasonable expectation of success. There has never been an identification as to why one of ordinary skill would reasonably expect success with the proposed combination. As discussed above, Uo's solutions are approximately 45-55 Vol.% methanol whereas Klein's solutions are approximately 65 Vol.% ethanol and moreover are heated to 80°C. The rejection contends that starting with Uo's already-toxic sol solution and increasing the concentration of the organic solvent, increasing the toxicity of the organic solvent (i.e., from methanol to ethanol), and increasing the temperature of the gelation solution would leave one of ordinary skill a reasonable expectation of success.

Since there is no reasonable expectation of success with the proposed combination, Applicants respectfully submit that a *prima facie* case of obviousness of claim 15 has not been established.

<u>Other Contentions Raised in Rejecting Claim 15</u>

Instead of seeking to establish a *prima facie* case of obviousness, a series of contentions have been made that have been thought to bear on the patentability of claim 15. For the sake of completeness, applicants now respond to these contentions.

A first such contention is that claim 15 encompasses the amount of organic solvent used by Klein. *See, e.g.*, page 7, line 19-20 of the action mailed August 24, 2004.

This contention is nothing more than a rehashing of the contention that the claims must expressly exclude an organic solvent, or at least some level of organic solvent. The fact that the present claims encompass the amount of organic solvent used by Klein is irrelevant. Applicants are entitled to claims as broad as the prior art and applicants' disclosure will allow. *In re Rasmussen*, 650 F.2d 1212, 1214 (Cust. & Pat.App. 1981). To hold otherwise would be to oblige applicants to claim the reasons why the references teach away from their combination, or to claim the reasons why one of ordinary skill would not be motivated to combine the references. To the best of Applicants' knowledge, no court has ever imposed such a requirement. Rather, the fact that the references teach away from their combination and that one of ordinary skill would not be motivated to combine the references with a reasonable expectation of success are, in and of themselves, sufficient to show that a *prima facie* case of obviousness has not been established.

A second such contention is that Uo describes that using a spore avoids the toxicity of an organic solvent. *See, e.g.,* page 8, line 4-7 of the action mailed August 24, 2004.

This contention presumably implies that Uo describes that his spores would survive the increased concentration of the organic solvent required by Klein to accommodate Klein's additional water, the increased toxicity of the organic solvent used by Klein, and the increased temperature of the gelation solution used by Klein.

Uo describes nothing of the sort. Instead, Uo describes that robust yeast cells are required to survive even his gelation solutions. Uo does not state or imply that even these robust yeast cells would survive the heightened concentration, toxicity, or temperature of Klein's gelation solutions.

Accordingly, claim 15 along with the claims dependent therefrom are not obvious over Uo, Hino, Klein, and Rao.

A check for the brief fee of $170 is enclosed.

Respectfully submitted,

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Date: 11/16/04

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Date: 11/18/04

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APPENDIX OF CLAIMS:

Claims 1-14. (Withdrawn)

Claim 15. A sol, comprising:

P moles of a hydroxy metallate;

W moles of water;

a sufficient amount of a dispersant to cause macropores in a gel formed by said sol; and

a biological material,

wherein a ratio of W:P is greater than 25:1.

Claim 16. The sol according to claim 15, wherein said dispersant comprises a water-soluble polymer.

Claim 17. The sol according to claim 15, wherein:

said hydroxy metallate is formed by hydrolysis of a sol-gel precursor.

Claim 18. The sol according to claim 17, wherein said sol-gel precursor comprises an alkoxy metallate.

Claim 19. The sol according to claim 15, wherein said alkoxy metallate comprises an alkoxy silicate.

Claim 20. The sol according to claim 15, further comprising a means for functionalizing a gel formed by condensation of said hydrolyzed species.

Claim 21. The sol according to claim 15, wherein said biological material comprises a cell.

Claim 22. The sol according to claim 21, further comprising nutrients configured to support said biological cell.

Claim 23. The sol according to claim 15, wherein said sol comprises a sol solution, said W moles of water forming at least 71 mole % of said sol solution.

Claim 24. The sol according to claim 17, further comprising an organic solvent comprising an organic by-product arising from the hydrolysis of said sol-gel precursor.

Claim 25. The sol according to claim 15, wherein a ratio of W:P is greater than 100:1.

Claim 26. A method, comprising:

mixing a vegetative cell into a sol;

mixing a sufficient amount of a dispersant into said sol to cause macropores in a gel formed by said sol; and

gelling said sol to form said gel.

Claim 27. (Withdrawn)

Claim 28. A gel, comprising:

a macroporous solid network formed by the condensation of hydroxy metallates from a sol solution; and

a bacterial cell added to the sol solution and thereby immobilized within said solid network,

wherein said sol solution is compatible with said bacterial cell.

Claim 29. A gel, comprising:

a solid network formed by the condensation of hydroxy metallates from a sol solution, the solid network defining macropores; and

a vegetative cell added to the sol solution and thereby immobilized within said solid network.

Claim 30. (Canceled)

Claim 31. The gel of claim 29, wherein said solid network transmits less than about 35% of a 700 nm light beam over a pathlength of about 0.9 cm when said macropores are filled with air.

Claim 32. The gel of claim 31, wherein said solid network transmits less than about 30% of said light beam when said macropores are filled with air.

Claim 33. The gel of claim 32, wherein said solid network transmits less than about 18% of said light beam when said macropores are filled with air.

Claim 34. The gel of claim 33, wherein said solid network transmits less than about 9% of said light beam when said macropores are filled with air.

Claim 35. The gel of claim 33, wherein said solid network is opaque to said light beam when said macropores are filled with air.

Claim 36. The gel of claim 29, wherein said vegetative cell is entrapped within said solid network.

Claim 37. The sol according to claim 21, wherein said cell comprises a bacterial cell.

Claim 38. The sol according to claim 21, wherein said cell comprises a vegetative cell.

Claim 39. The method of claim 26, wherein mixing the vegetative cell into the sol comprises mixing the vegetative cell into the sol including P moles of a hydroxy metallate and W moles of water, wherein a ratio of W:P is greater than 25:1.